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Original contribution

Perioperative dexmedetomidine reduces delirium after cardiac surgery: A meta-analysis of randomized controlled trials

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ABSTRACT

Study objective: To evaluate the efficiency of dexmedetomidine on the incidence of delirium in patients after cardiac surgery.
Design: Meta-analysis of randomized controlled trials.
Setting: Operating room and Intensive Care Unit (ICU).
Patients: Ten trials with a total of 1387 patients undergoing cardiac surgery met the inclusion criteria.
Intervention: Randomized controlled trials (RCTs) comparing the effect of dexmedetomidine versus non-treatment of dexmedetomidine (normal saline (NS), propofol and other anesthetic drugs) on delirium in patients undergoing cardiac surgery were retrieved from PubMed/Medline, Embase, the Cochrane Library and Web of science. The primary outcome was the incidence of delirium. The secondary outcomes were the rate of bradycardia and hypotension, the duration of mechanical ventilation and the length of ICU and hospital stay.
Main results: Compared with the control group, Dexmedetomidine significantly decreased the incidence of postoperative delirium, (risk ratio 0.46; 95% confidence intervals, 0.34 to 0.62; $P < 0.00001$), while the incidence of bradycardia was increased in dexmedetomidine group (risk ratio 1.86; 95% confidence intervals, 1.16 to 2.99; $P = 0.01$). There was no significant difference between groups with regarding to the occurrence of hypotension (risk ratio 0.90; 95% confidence intervals, 0.59 to 1.38; $P = 0.63$), the duration of mechanical ventilation (Mean Difference 0.21; 95% confidence intervals, −0.70 to 1.12; $P = 0.65$), and the length of ICU (Standard Mean Difference − 0.07; 95% confidence intervals, −0.19 to 0.06; $P = 0.3$) and hospital stay (Mean Difference − 0.13; 95% confidence intervals, −0.56 to 0.30; $P = 0.56$).
Conclusion: Perioperative dexmedetomidine administration decreased the incidence of delirium in patients after cardiac surgery, but might increase the rate of bradycardia. Furthermore, we did not observe significant differences in the incidence of hypotension, the duration of mechanical ventilation and length of ICU and hospital stay between groups. Future studies are needed to ascertain the effect of dexmedetomidine on the incidence of delirium after coronary artery bypass grafting (CABG) and in patient with cognitive disorder at baseline, whether intraoperative dexmedetomidine infusion could reduce postoperative delirium and the optimal dose of dexmedetomidine.

1. Introduction

Delirium, which involves acute disorder of cognition, attention and perception, is a common and life-threatening complication among patients who are 65 years of age or older [1]. The prevalence of delirium is extremely higher in patients after cardiac surgery, with reported incidences of 20 to 50% [2, 3]. Known risk factors for the development of delirium after cardiac surgery include advanced age, multiple coexisting conditions, deep sedation, complicated surgery process and high pain levels [4–6]. Furthermore, the occurrence of delirium has been believed to increase postoperative complications and mortality, prolong length of Intensive Care Unit.

(ICU) and hospital stay, as well as decline cognitive function [7–9]. Although non-pharmacologic approaches including early mobilization, sleep enhancement and orientation to time and place for delirium prevention seem to be effective, there are still limitations of these interventions under some certain circumstance [10, 11]. As a result, a number of pharmacologic approaches including dexmedetomidine and other prophylactic antipsychotics have been estimated in clinical researches, but there is still no convincing evidence that any of these methods has effectively reduced the incidence of postoperative delirium [10, 12–15].

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Dexmedetomidine is a highly selective α_2-adrenoceptor agonist, with sedative, analgesic-sparing, anxiolytic and sympatholytic properties, and minimal respiratory depression. Moreover, it is also used for sedation of ICU patients during mechanical ventilation (MV) and has been reported to reduce length of ICU stay and duration of mechanical ventilation [16]. Besides, bradycardia and hypotension are common side effects of dexmedetomidine. Notably, several clinical researches have shown that perioperative dexmedetomidine administration decreased the incidence of delirium in patients after cardiac surgery [17–19]. However, others could not arrive at the similar conclusion [20–22]. It is far from unanimous in the efficacy of dexmedetomidine on postoperative delirium. Therefore, this meta-analysis was conducted to evaluate the efficiency of perioperative dexmedetomidine (versus normal saline or other anesthetic drugs) infusion on the incidence of delirium in patients after cardiac surgery.

2. Materials and methods

This meta-analysis was conducted in accordance with the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
(PRISMA) [23].

2.1. Search strategy and eligible criteria

Relevant researches published between Jan 1, 1990 and April 5, 2018, were systematically searched by the following databases: Pubmed/Medline, Embase, the Cochrane Library/Central and Web of science. The references of included researches were also examined. According to the search strategy, both MeSH terms and free terms were used. A basic search strategy was conducted using the following terms: (dexmedetomidine OR “dexmedetomidine”[MeSH]) AND (delirium OR “Delirium”[MeSH]) AND (“cardiac surgery” OR “heart surgery” OR valve OR CPB OR “cardiopulmonary bypass” OR CAB OR “coronary artery bypass”) search All Fields.

Studies restricted to Randomized controlled trials (RCTs), published in English and compared the effect of dexmedetomidine with normal saline (NS) or other anesthetic drugs on the incidence of delirium after cardiac surgery were included.

2.1.1. Exclusion criteria

Pediatric surgery, non-cardiac surgery, non-intravenous administration of dexmedetomidine and animal experiments were excluded from this meta-analysis.

2.2. Data extraction and quality assessment

Data extraction and quality assessment were completed by 2 authors (Wu and Dai) independently. One author (Wu) then entered these information into the table and checked for consistency and completeness. Disagreements on data extraction and quality assessment were handled by discussion until a consensus was reached. The extracted date and information were as follows: first author, year of publication, surgery type, the duration of cardiopulmonary bypass (CPB), timing and dose of dexmedetomidine and the control group and methods of delirium assessment. The following adverse events including delirium, bradycardia and hypotension, the length of ICU and hospital stay and the duration of mechanical ventilation were extracted as well.

Quality assessment of included RCTs was performed according to PRISMA. There are seven sections of this assessment, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each section was classified into low, high, or unclear risk of bias.

2.3. Endpoints

The primary end point of this meta-analysis was the incidence of delirium after cardiac surgery. The secondary outcomes were the incidence of bradycardia and hypotension, as well as the length of hospital and ICU stay and the duration of mechanical ventilation.

2.4. Statistical analysis

For dichotomous data (incidence of delirium, bradycardia and hypotension), Mantel-Haenszel method was used to combine outcomes and risk ratio (RR) with 95% confidence interval (CI) were calculated. With regard to continuous variables (length of hospital and ICU stay, the duration of mechanical ventilation), Inverse-Variance method was used and mean difference (MD) or standardized mean difference (SMD) with 95% CI were calculated. For studies where no events were observed in one arm, a fixed value 0.5 was added to the corresponding cells. According to Cochrane Handbook, the approach to including a study with two intervention or control groups is to combine them into a single group. For dichotomous outcomes, both the sample sizes and the numbers of patients with events were summed across groups. For continuous outcomes, means and standard deviations can be combined using specific formula. If a continuous variable presented as median and interquartile range (IQR) or median and 95% confidence interval (CI) and the sample sizes are large enough ($N > 100$), standard deviations (SD) equals to IQR/1.35 or $\sqrt{N} \times$ (upper limit − low limit) / 3.92 respectively. Heterogeneity was evaluated with chi-squared test and I^2 value > 50 represents significant heterogeneity of intervention effects. If there was no heterogeneity, fixed effect model can be used. When substantial Heterogeneity was observed, random effect model was utilized [24]. Subgroup analyses were used to find the source of Heterogeneity. We also preformed several sensitivity analyses to evaluate the robustness of the results. Publication bias was evaluated by conducting a funnel plot. The symmetry of funnel plot was assessed with Egger's tests and $P < 0.1$ was regarded as statistically significant. Statistic difference was defined as $P < 0.05$(two sides). All statistical analyses were performed by Revman 5.3 and Stata 15.

3. Results

3.1. Search results and characteristics of included studies

According to the search strategy, a total of 291 trails were identified. Among them, 48 studies were removed due to duplication. Other 233 studies were excluded on base of inclusion and exclusion criteria. 10 RCTs including 1387 patients were ultimately included in this meta-analysis. The flow chart of selection processes was shown in (Fig. 1). Methodological quality assessment was conducted according to Cochrane Risk of Bias Methods and the result was summarized in (Fig.2). The major characters of these eligible studies were extracted and presented in (Table 1). Two of the included studies were coronary artery bypass grafting (CABG) [21, 25], three trials were valve surgery [17, 20, 26] and the other five studies were combined CABG and valve surgery [18, 19, 22, 27, 28]. Furthermore, 3 studies used propofol as control [18, 25, 26], 4 used normal saline (NS) [20–22, 27], two used remifentanil and morphine respectively [19, 28], whereas one used midazolam and propofol [17]. The timing and dosing of dexmedetomidine administration were varied between included studies. After a loading dose (0.4–1 μg/kg), dexmedetomidine was continuously infused at a speed of 0.1 to 0.8 μg/kg/h in 6 trials [17–20, 22, 25]. 4 studies administrated dexmedetomidine continuously at a rate of 0.04 to 5 μg/kg/h without loading dose [21, 26–28].

3.2. Primary outcome of the pooled studies

This meta-analysis revealed that dexmedetomidine significantly